REMARKS

Telephone Interview with Examiner

Applicants first wish to express their sincere appreciation for the time that Examiner Sisson spent with Applicants' Attorney Cynthia Lee during a telephone discussion on January 10, 2006 regarding the outstanding Final Office Action. Applicants believe that certain important issues were identified during the telephone discussion, and that they are resolved herein. During that conversation, the Examiner seemed to indicate that it would be beneficial for Applicants to make the amendments herein. Specifically, the Examiner agreed to consider the amendments to claim 10 herein with respect to the rejections under 35 U.S.C. §112, 1st paragraph. Thus, Applicants respectfully request that Examiner carefully consider this response and the amendments. If the Examiner has any questions about the instant Response, the Examiner is invited to telephone the undersigned to resolve any outstanding issues.

Cancellation of Claims

Claims 17-18 are canceled herein without prejudice, waiver, or disclaimer. Applicants take this action merely to reduce the number of disputed issues and to facilitate early allowance and issuance of other claims in the present application. Applicants reserve the right to pursue the subject matter of the canceled claims in a continuing application, if Applicants so choose, and do not intend to dedicate any of the canceled subject matter to the public.

Specification

The specification has been objected to because documents have been allegedly improperly incorporated by reference, and further in that the amendments filed on 28 February 2005 allegedly introduced new subject matter. *See Office Action* at 2-4. The specification has been amended herein to cancel the incorporations by reference and the matter introduced in the previous amendment. Applicants submit that the objections have been obviated and respectfully request that they be withdrawn.

Response To Claim Rejections Under 35 U.S.C. §112, First Paragraph

(a) Claims 10-14, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 17-18 are canceled without prejudice, waiver, or disclaimer, thus rendering the rejection of those claims moot.

With respect to the rejection of claims 10-14, the Office alleges that "[t]here is no further requirement as to how the 'first plurality' is immobilized." *Office Action* at 5. Applicants have amended claim 10 herein to add that the first plurality "is immobilized on a surface such that the different sequences of the first plurality of nucleic acids can be differentiated by location." Applicants submit that the signals generated would also be differentiated by location as well. It would be well within the skill of one in the art to know how to immobilize the first plurality on the substrate or surface. Indeed, the specification teaches that "[i]mmobilization of oligonucleotides on a substrate or surface may be accomplished by well-known techniques, commonly available in the literature." *Specification* at 15, lines 5-10. Further the specification lists some exemplary references teaching the immobilization of oligonucleotides.

Further, the Office asserts that "[w]ith every member of the first group and every member of the second group being different from every other member, the level of detection is ultimately on the level of a single molecule. A review of the disclosure fails to find the requisite...description of where one would be able to detect single molecules." *Office Action* at 5. Applicants respectfully traverse. The language in question of claim 10 was found in the originally-filed specification, also in claim 10. As held by Court of Appeals for the Federal Circuit, "disclosure in an originally-filed claim satisfied the written description requirement." *Union Oil Co. of Calif. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000) (citing *In re Gardner*, 480 F.2d 879, 880, 175 USPQ 149 (CCPA 1973), which held "Under these circumstances, we consider the original claim in itself adequate 'written description' of the claimed invention. It was equally a 'written description'...whether located among the original claims or in the descriptive part of the specification."). Thus, the originally-filed claim 10 provided the written description for the language of claim 10 that recites that every member of the first plurality is different for other members of the first plurality, and each first region of each second nucleic acid being a different sequence from other first regions of other nucleic acids in the second plurality. Applicants therefore respectfully request that the rejection be withdrawn.

In addition, no where does the specification refer to a single molecule. It would be understood by one skilled in the art upon reading the specification and claims that Applicants are not claiming a single nucleic acid that is positioned at each location. Nevertheless to facilitate prosecution and early allowance of the claims, Applicants have amended claim 10 herein to recite that "different sequences of the first plurality of nucleic acids can be

differentiated by location, wherein the nucleic acid at each location has a different sequence than nucleic acids at other locations" and that "wherein each first region of each ~~second~~ nucleic acid at a particular location has a different nucleotide sequence from other first regions of other nucleic acids in the second plurality at other locations." Applicants submit that the amendments do not constitute new matter. Support for the amendments can be found in the specification at least at the following passage: "[t]he set of oligonucleotides for the array are attached to a solid support... such that different sequences of oligonucleotides can be differentiated by location. For example each position on a glass slide corresponds to a specific nucleic acid sequence." *Specification* at 19, lines 1-5. That is not to say that each position corresponds to a single molecule, just a specific nucleic acid sequence, which sequence can be expressed by a multitude of molecules.

Based on the foregoing, Applicants respectfully request that the above rejection of claims 10-14 be withdrawn.

(b) Claims 10-14, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 17-18 are canceled without prejudice, waiver, or disclaimer, thus rendering the rejection of those claims moot.

With respect to claims 10-14, the Office asserts that "[t]he claims place no restriction on the density of the nucleic acids at each of the array spots, the proximity of one spot to another, the length of the immobilized nucleic acids, or on the length of the target sequences." *Office Action* at 7. The Office Acton then lists art-recognized problems with hybridization assays and concludes "[t]he instant disclosure is essentially silent as to how these art-recognized issues would be overcome." *Id.* at 10. Applicants respectfully traverse.

First, Applicants submit that even though there may be art-recognized issues with hybridization assays, the Applicants have nevertheless enabled one skilled in the art to practice the claimed method. Put another way, the art of hybridization assays (as admitted by the Examiner) has become very developed and one skilled in the art would understand process parameters that can be varied to enable one to practice the method. As recited by one treatise:

> If the relevant art is one in which the starting materials are somewhat variable, or in which the process parameters are not easily controlled, and in which the set-up of production facilities therefore typically involves some amount of trial-and-error, the patent disclosure can leave some amount of experimentation to the reader.

2 Moy's Walker on Patents § 7:20 (4th ed.) (citing, *e.g., Minerals Separation v. Hyde*, 242 U.S. 261, 270-71, 37 S. Ct. 82, 61 L. Ed. 286 (1916); *Mowry v. Whitney*, 81 U.S. 620, 644, 20 L. Ed. 860 (1871); *Exxon Res. and Eng'g Co. v. U.S.*, 265 F.3d 1371, 1379, 60 U.S.P.Q.2d 1272 (Fed. Cir. 2001); *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 37 U.S.P.Q.2d 1618 (Fed. Cir. 1996); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 U.S.P.Q. 303 (Fed. Cir. 1983); *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984)) (emphasis added).

The Applicants have disclosed at least one embodiment for the claimed method, and thus the application has fulfilled the enablement requirement. *See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334-37, 65 U.S.P.Q.2d 1385, 1400-02 (Fed. Cir. 2003) (affirming district court's ruling that claims direct to a DNA product were enabled where patent described at least one way to make claimed product, fact that patent did not disclose later developed method to make product as used by the accused infringer was irrelevant to the enablement inquiry, and district court made fact-findings that were not clearly erroneous that "any gaps between the discloses and the claim breadth could easily be bridged." (emphasis added)).

Second, the Applicants are not silent as to how the art-recognized issues would be overcome, as asserted by the Office. Indeed, the Applicants have determined the following:

> disadvantages of the assay include cross hybridization between probes and unintended targets (non-cognate interactions) mediated through target-target interactions, and cross hybridization directly between probes and unintended targets. These types of non-cognate interactions introduce error into the measurements.

Specification at 21, lines 11-17. Furthermore, the specification states:

> Undesirable cross hybridization between anti-target sequences and anti-tag sequences reduces the signal and sensitivity of the assay by reducing the amount of intermediary molecules available for sorting target molecules, and also reduces the anti-tag sites available on the array for sorted target molecules. Therefore, cross hybridization between the array-bound anti-tag molecules and anti-target regions of intermediary molecules reduces the multiplexing rate obtainable by the universal tag system.

Id. at 23, lines 6-12. In summary, as of the filing of the application, Applicants submitted that "[t]o date, there are no teachings that address the problem of cross-hybridization between anti-tag molecules and anti-target domains of the intermediary molecules." *Id.* at 24, lines 5-7.

Applicants have overcome these art cited problems by employing "polynucleotides containing UNA [that] are capable of selectively hybridizing to a complementary polynucleotide without hybridizing to complementary polynucleotide having the same base sequence, but containing modifications of the base [unstructured nucleic acids] (UNAs)." *Id.* at 25, lines 7-13. Applicants then proceed to list generic concepts of the UNA base-pairing schemes on pages 25-27 of the specification, and this specific examples of nucleic acid analogs on pages 28-32. The Applicants then conclude with how certain art issues have been overcome by the utilizing the disclosed UNAs in the claimed method, by for example, lowering the melting temperature. *See, e.g., id.* at 32, lines 7-14 ("introducing either P or I into 28-mer duplexes to form P/G and I/C base-pairs decreased the Tm of the duplex by -0.5 and 1.9° C respectively per modified base-pair. These values reflect the slight destabilization attributable to the G/P pair and a larger destabilization due to the I/C pair. However, introducing P and I into the duplexes such that opposing I/P base-pairs are formed reduced the Tm by -3.3° C per modified base-pair. Therefore the I/P base pairs are more destabilizing.").

In addition, claim 10 as amended recites that "each second nucleic acid of the second plurality is known." Applicants believe that one skilled in the art upon reading the specification would find support for the claimed feature that the nucleotide sequence of the nucleic acids of the second plurality would be known . In particular, the specification at FIG. 1A and FIG. 2 depict a sandwich-type hybridization assay. As conventionally known, the nucleotide sequences of the probe and the intermediate molecule are known. Therefore, when a label is attached to a target molecule and the target molecule hybridizes to the probe or intermediate molecule and the label is detected, then the nucleotide sequence, or a portion thereof, of the target molecule can be determined. The specification refers to a number of different references that explain in detail how a hybridization array works, and how the sequence of a probe and the sequence of any intermediate molecule is "known" when interrogating a biological sample or target. For example, the specification states as follows:

> Genotyping of single nucleotide polymorphisms (SNPs) using highly multiplexed DNA array-based methods are well known (for a review, see Syvanen. Human Mutation 13:1-10, 1999). For example, Pastinen et al. (*Genome Research*. 7:606-614, 1997) used oligonucleotide arrays to detect sequence mutations through single nucleotide primer extension of array-based oligonucleotides that hybridize adjacent to a sequence of interest in a target nucleic acid. Ross et al. (Nature Biotechnology. 16:1347-1351, 1998) describe multiplex genotyping using DNA arrays using mass spectrometry. In addition, a review by Hacia (Nature Genetics. 21:42-47, 1999) describes methods of resequencing and mutational analysis using DNA oligonucleotide

> arrays. These references describing SNP genotyping are incorporated herein by reference.
> ...
>
> An alternative array-based method of analyzing nucleic acids has been described by several groups (Brenner U.S. Pat. No. 5,604,097; Morris et al. EP 97302313), and uses a universal spatially addressable array. In this method, the sequence of the oligonucleotides on an array are fixed, and thus are not tailored for each biological sample to be assayed. The universal nature of the arrays allows the same array design to be used with multiple samples having different target nucleic acid sequences.
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> To analyze and detect nucleic acids in a sample, methods using a fixed array design rely on the use of an intermediate nucleic acid molecule which hybridizes to a target nucleic acid molecule with one region ("anti-target") and also hybridizes to an oligonucleotide probe on the fixed array with another region ("tag"). The intermediary molecules therefore contain two domains that perform the two functions of 1) binding to a target molecule and 2) sorting the target molecules by binding to a spatially addressed probe ("anti-tag") on the fixed array. These two steps can be performed, in any order, separately or simultaneously. Thus the fixed array of oligonucleotides is designed to provide a substrate for sorting target molecules.

Specification at page 20, line 16 - page 21, line 3 and page 21, line 18 - page 22, line 9.

Therefore, Applicants have provided one skilled in the art of hybridization assays with the ability to synthesize the anti-target and anti-tag nucleic acids (see Examples, page 40-45) with unstructured nucleic acids that reduce cross-hybridization, immobilize the anti-tag nucleic acids at locatable spots, introduce a biological sample, and correlate detected signals from the sample or tag sequence at a location with a sequence. Specific process parameters are easily determined by one skilled in the art. Therefore, Applicants respectfully request that the rejection claims 10-14 for lacking enablement be withdrawn.

CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicants respectfully submit that all objections and rejections have been traversed, and/or accommodated, and that the now pending specification and claims 10-14 are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned agent at (770) 933-9500.

Respectfully submitted,

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